UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,592	03/24/2006	Yusuke Nakamura	082368-003610US	4468

20350 7590 10/15/2008

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,592	NAKAMURA ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1,3,6 and 8-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5,7,27 and 28* is/are rejected.

7)☒ Claim(s) *27 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/24/06, 7/20/07, 3/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed July 11, 2008 in response to the Office Action of June 12, 2008 is acknowledged. Applicant elected with traverse Group II, claims 2-5, 7, 27, and 28, and the species SEQ ID NO:2 (encoded by SEQ ID NO:1).

2. Applicants argue that they amended the claims and the new technical feature linking the Groups is now "a polypeptide comprising an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO:2 or 4 and that has biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 or 4". Applicants argue that Rosen et al teaches SEQ ID NO:2022 which only has 61% identity to SEQ ID NO:2 of the instant application, therefore it does not teach the new technical feature linking the Groups. Applicants point to Example 39 of the PCT International Search and Preliminary Examination Guidelines and argue Groups I and II should be rejoined because Group II is drawn to a polynucleotide that encodes the polypeptide of Group I and they share the same technical feature (p. 11-12).

The arguments have been considered but are not found persuasive. Based on Applicants' amendments, the inventions listed as Groups I-XVIII still do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking Groups I-XVIII appears to be a polypeptide comprising an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO:2 or 4 and that has biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 or 4.

However, said technical feature does not constitute a special technical feature in view of GenBank Accession No. BQ71560 and BQ672221, publicly available July 15, 2002, and each teach a polynucleotide that encodes a polypeptide that has a sequence that is 100% identical to SEQ ID NO:2 of the instant application (see sequence search result #4 and #6, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst"). Given the polynucleotides BQ71560 and BQ672221 encode a polypeptide comprising an amino acid sequence having100% homology to SEQ ID NO:2 of the instant application, the polypeptide encoded would have biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2.

Therefore, the technical feature linking the inventions of Groups I-XVIII does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Accordingly, Groups I-XVIII are not so linked by the same or a corresponding special technical feature as to form a single general incentive concept and restriction for examination purposes as indicated is proper. Thus, the "special technical feature" does not define a contribution over the prior art. For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Claims 1-28 are currently pending. Claims 1, 2, 12, 15, , 18, 19, 21, 22, 24, 25, 27 are amended. Claims 1, 3, 6, and 8-26 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 2, 4, 5, 7, 27, and 28 as drawn to SEQ ID NO:2 are currently being examined.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 24, lines 15 and 28, and page 41, line 28. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. Claims 27 and 28 are objected to because of the following informalities: There are grammatical errors in the claims. Claim 27 should list parts (a) and (b) in the alternative or recite "a polynucleotide encoding a polypeptide selected from the group consisting of" (a) and (b). Examiner suggests amending claim 28 to recite "wherein the polynucleotide is incorporated **into an** expression vector". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 4, 5, and 7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 4 and 5 read on cells found in intact mammals, including humans that received the vector. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since a host cell does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" in connection with the host cell to identify a product that is found in nature.

Claim 7 reads on a polynucleotide that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since a polynucleotide does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the polynucleotide to identify a product that is found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2, 4, 5, 7, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to an isolated polynucleotide encoding a substantially pure polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; and (b) a polypeptide that comprises **an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2** (claim 2), vectors and host cells comprising said polynucleotide (claims 4, 5), **a polynucleotide that is complementary to the complementary strand of the polynucleotide of claim 2 or to the complementary strand thereof and that comprises at least 15 nucleotides** (claim 7), and pharmaceutical compositions comprising said polynucleotide or vector (claims 27, 28).

The specification discloses that three variant transcripts were identified as up-regulated in pancreatic cancer cell line Capan-1 including C1958V1 ad C1958V2 (p. 4, lines 29-35). The specification discloses C1958V1 is encoded by the open reading frame of SEQ ID NO:1, encoding a 76 amino acid protein SEQ ID NO:2 (p. 5, lines 20-24). C1958V2 includes a putative 20 amino acid protein encoded by the reading frame of SEQ ID NO:3, encoding SEQ ID NO:4 (p. 5, lines 28-31). The specification discloses that "functionally equivalent" means that the polypeptide has the activity to promote cell proliferation like C1948V1 or C1958V2 protein and to confer oncogenic activity to cancer cells. Other than SEQ ID NO:1, the specification does not disclose any other

polynucleotide encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2, as broadly encompassed in the claims. The claims encompass polynucleotides of unknown sequence encoding polypeptides with any 20% or less of their sequence structure unknown and having any undefined biological activity of SEQ ID NO:2. Claim 7 further encompasses a broad genus of polynucleotides that are at least 15 nucleotides long comprising any unknown sequence with any portion complementary to any sequence of a polynucleotide of claim 2 or to the complementary strand thereof. The complement is not required to be the complete complement or even fully complementary.

The art teaches polynucleotides encoding a polypeptide that comprise an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 (see GenBank Accession Nos. BQ71560, BQ672221, and BI914593), however these polynucleotides do not provide an adequate representative number of species to support adequate written description for the broad genus of polynucleotides encoding a polypeptide that comprise an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2, or the broad genus of complements as encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of a polynucleotide encoding a polypeptide that comprises "an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2" and "a polynucleotide that is complementary to the complementary strand of the polynucleotide of claim 2 or to the complementary strand thereof and that comprises at least 15 nucleotides". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because

> it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. Thus, the instant specification may provide an adequate written description of polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 or complements, per Lilly by structurally describing representative polynucleotides or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses polynucleotide SEQ ID NO:1 that encodes protein

SEQ ID NO:2, this does not provide a description of the broadly claimed polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2, or complements that would satisfy the standard set out in Enzo because the specification provides no structural features coupled to functional characteristics. In the instant claims, according to the Enzo standard, the claimed polynucleotides do not have a conserved structural feature coupled to the function of "a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2". There is only a recitation of 80% or higher homology, and which of the 80% that must be homologous or conserved for the biological activity is not disclosed or recited.

Further, the specification also fails to describe polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2, or complements by the test set out in Lilly because the specification describes only SEQ ID NO:1 that encodes protein SEQ ID NO:2. Therefore it necessarily fails to describe a representative number of such species. In the instant claims, one of skill in the art cannot visualize or recognize the identity of the members of the genus of polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of

SEQ ID NO: 2 because there is no identification of which sequences of the 80% must be conserved among the genus for the required biological activity. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Thus, the specification does not provide an adequate written description of a polynucleotides encoding a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2, or complements that is required to practice the claimed invention.

8. Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a **pharmaceutical** composition **for treating or preventing pancreatic cancer** comprising a **pharmaceutically** effective amount of a polynucleotide encoding the polypeptide: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2 or a fragment thereof; (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO:2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2, or fragment thereof as an active ingredient, and a pharmaceutically acceptable carrier (claim 27), the **pharmaceutical** composition of claim 27, wherein the polynucleotide is incorporated in an expression vector (claim 28).

The specification discloses a pharmaceutical composition for treating cell proliferative disease such as cancer and the pharmaceutical composition may be, for example, an anti-cancer agent. The pharmaceutical composition is used to inhibit the growth of cancerous cells and may be applied to humans and domesticated mammals (p. 7, line 31 through p. 8, line 10; p. 36, line 36 through p. 37, line 7). The specification

discloses isolated gene from humans, C1958V1, that includes a polynucleotide sequence as described in SEQ ID NO:1 that encodes polypeptide SEQ ID NO:2 (p. 5, lines 17-27; p. 6, lines 1-2). Several up-regulated genes were found in human pancreatic cancer cells including "C1958" that was upregulated in 70% of pancreatic cases and through screening of a cDNA library made from pancreatic cancer cell line, Capan-1, three variant transcripts of C1958 were found, one of which is C1958V1 encoding a 76 amino acid protein (p. 4, lines 29-33). Reduction of expression of C1958V1 by transfection of specific antisense S-oligonucleotides or small interfering RNAs inhibited the growth of pancreatic cell lines *in vitro* (p. 5, lines 3-5; Figure 5; p. 42, line 29 through p. 43, line 11). The specification discloses that C1958V1 proteins have the activity of promoting cell proliferation (p. 31, lines 9-10 and 18-19). The specification contemplates administering C1958V1 protein or a polynucleotide encoding the protein or fragments thereof to induce anti-tumor immunity (p. 34, lines 7-30).

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide examples for the claimed polynucleotide predictably functioning as a pharmaceutical for the treatment or prevention of pancreatic cancer or for inducing anti-tumor immunity to treat cancer as claimed and contemplated. The specification contemplates administering a polynucleotide encoding C1958V1 for inducing anti-tumor immunity and demonstrates that siRNA reduced C1958V1 mRNA expression and reduced cell growth *in vitro*. The specification also discloses that C1958V1 expression promotes cell growth. Given C1958V1 expression promotes cell growth, one of skill in the art could not reasonably

extrapolate the teaching of the specification to the enablement of the pharmaceutical as claimed because the claimed polynucleotide and vector comprising it would reasonably function to express C1958V1 and promote cell growth when administered. The specification has not provided guidance or examples for the claimed pharmaceutical functioning to inhibit cell growth by inducing any anti-tumor immune response.

One of skill in the art could not reasonably extrapolate the results of the administration of siRNA *in vitro* to cell lines to the pharmaceutical properties of a C1958V1 polynucleotide *in vivo* because the example is not commensurate in scope with the claimed polynucleotide acting pharmaceutically as claimed and contemplated. For example, siRNA functions to inhibit RNA expression, however, the claimed polynucleotide pharmaceutical is not an siRNA and does not function to inhibit C1958V1 mRNA expression, but rather would promote it. Further, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Zips et al. (2005, In Vivo, 19:1-7) teach "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant

and non-malignant cells. Vascularization, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential (p. 3, col. 2)."

Additionally, the specification does not disclose which variant of the three C1958 variants is expressed in pancreatic tumors *in vivo* and which of these variants is expressed and promote cell growth *in vivo*. The specification only discloses the isolation of C1958V1 and variants from a single pancreatic cancer cell line cultured *in vitro*. The teachings of Stein et al (Cancer Research, April 2004, 64:2805-2816) demonstrate that differences between the tumor cell of a subject and a cultured tumor cell line includes vast differences in gene expression (see pages 2809 and 2811, in particular). Specifically, Stein et al found that, "...compared with cell lines, solid tumors (a) overexpress genes concerned with cell-cell communication and with the ECM (Table 2); (b) overexpress genes involved in the immune response (Table 2); and (c) underexpress genes involved in protein synthesis (Table 3)" (see right column of page 2814, in particular). It is not clear whether the C1958V1 variant polynucleotide from the derived pancreatic cell line is an artifact of the cell culture system of the tumor cells cultured *in vitro* or whether the C1958V1 polynucleotide can be in any way related to C1958 mRNA found in *in vivo* tumor cells from which the cell line was derived in view of the art recognized problems with artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of

Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in vivo* cancer cells have been established and even for the bona fide cancer cell lines it in difficult to prove that the immortalized cells originated from a specific cancer cell (see abstract). It is clear that the unpredictability of using cancer cell lines is well known in the art since Slamon et al, (Cancer Cells, 1989, 7:371-384) specifically teach that for their studies they use clones from actual human tumor tissue because DNA in cell lines can acquire genetic changes *in vitro* that may not be representative of the gene *in vivo*, p. 373, col 1). Thus, based on the cell culture data presented in the specification, in the absence of data provided from primary tumor cells, no one of skill in the art would believe it more likely than not that the claimed invention would have function as a pharmaceutical composition for the treatment and prevention of pancreatic cancer. A high quantity of experimentation is necessary to practice the invention as claimed.

MPEP 2164.03 states: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily

anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. Given the state of the art stated above, one of skill in the art would not extrapolate the results of the *in vitro* assay to the enablement of the claimed polynucleotide composition to function predictably as a pharmaceutical.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 2 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. BQ71560, publicly available July 15, 2002 (see NCBI Sequence Viewer for BQ71560, p. 1-2 and "Revision History for BQ71560", p. 1) (see also sequence search result #4, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst").

The claims are drawn to an isolated polynucleotide encoding a substantially pure polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; and (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 (claim 2), a polynucleotide that is complementary to the complementary strand of the polynucleotide of claim 2, and that comprises at least 15 nucleotides (claim 7).

GenBank Accession No. BQ71560 teaches a polynucleotide that encodes a polypeptide that has a sequence that is 100% identical to SEQ ID NO:2 of the instant application (see sequence search result #4, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst"). Given the polynucleotide BQ71560 encodes a polypeptide comprising an amino acid sequence having100% homology to SEQ ID NO:2 of the instant application, the polypeptide encoded would have biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 as claimed. Given the polynucleotide of BQ71560 encodes a polypeptide comprising an amino acid sequence 100% identical to SEQ ID NO:2, the polynucleotide would be complementary to the complementary strand of the polynucleotide of instant claim 2, and does comprise at least 15 nucleotides.

11. Claims 2 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. BQ672221, publicly available July 15, 2002 (see NCBI Sequence Viewer for BQ672221, p. 1-2 and "Revision History for BQ672221", p. 1) (see also sequence search result #6, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst").

The claims are drawn to an isolated polynucleotide encoding a substantially pure polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; and (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 (claim 2), a polynucleotide that is complementary to the complementary strand of the polynucleotide of claim 2, and that comprises at least 15 nucleotides (claim 7).

GenBank Accession No. BQ672221 teaches a polynucleotide that encodes a polypeptide that has a sequence that is 100% identical to SEQ ID NO:2 of the instant application (see sequence search result #6, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst"). Given the polynucleotide BQ672221 encodes a polypeptide comprising an amino acid sequence having100% homology to SEQ ID NO:2 of the instant application, the polypeptide encoded would have biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 as claimed. Given the polynucleotide of BQ672221 encodes a polypeptide comprising an amino acid sequence 100% identical to SEQ ID

NO:2, the polynucleotide would be complementary to the complementary strand of the polynucleotide of instant claim 2, and does comprise at least 15 nucleotides.

12. Claims 2 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. BI914593, publicly available October 16, 2001 (see NCBI Sequence Viewer for BI914593, p. 1-2 and "Revision History for BI914593", p. 1) (see also sequence search result #8, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst").

The claims are drawn to an isolated polynucleotide encoding a substantially pure polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; and (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 (claim 2), a polynucleotide that is complementary to the complementary strand of the polynucleotide of claim 2, and that comprises at least 15 nucleotides (claim 7).

GenBank Accession No. BI914593 teaches a polynucleotide that encodes a polypeptide that has a sequence that is 88.6% identical to SEQ ID NO:2 of the instant application with 100% local similarity (see sequence search result #8, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst"). Given the polynucleotide BQ672221 encodes a polypeptide comprising an amino acid sequence

that has 80% or higher homology to SEQ ID NO:2 of the instant application, the polypeptide encoded appears to be the same polypeptide instantly claimed, hence, would have biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 as claimed. Given the polynucleotide of BI914593 encodes a polypeptide comprising an amino acid sequence 88.6% identical to SEQ ID NO:2, the polynucleotide would be complementary to the complementary strand of the polynucleotide of instant claim 2, and does comprise at least 15 nucleotides.

The reference does not specifically teach that the polynucleotide encodes a polypeptide that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2. However, the claimed polynucleotide appears to be the same as the prior art polynucleotide, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 2, 4, 5, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BQ71560, publicly available July 15, 2002 (see NCBI Sequence Viewer for BQ71560, p. 1-2 and "Revision History for BQ71560", p. 1) (see also sequence search result #4, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst"), in view of Ausubel et al, Current Protocols in molecular Biology, 1995, 3rd edition, Wiley & Sons, NY, Section9, p. 9-1 to 9-14).

The claims are drawn to an isolated polynucleotide encoding a substantially pure polypeptide selected from the group consisting of: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; and (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 (claim 2), a host cell harboring the polynucleotide if claim 2 or a vector comprising the polynucleotide (claim 4), a method for producing the polypeptide of claim 1, comprising (a) culturing the host cell of claim 4; (b) allowing the host cell to express the polypeptide; and (c) collecting the expressed polypeptide (claim 5), a pharmaceutical composition for treating or preventing pancreatic cancer

comprising a pharmaceutically effective amount of a polynucleotide encoding the polypeptide: (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; (b) a polypeptide that comprises an amino acid sequence that has 80% or higher homology to the amino acid sequence of SEQ ID NO: 2 and that has a biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2 or fragment thereof as an active ingredient, and a pharmaceutically acceptable carrier (claim 27), the pharmaceutical composition of claim 27, wherein the polynucleotide is incorporated into an expression vector (claim 28).

It is noted that the preamble recitations of "pharmaceutical" and "for treating or preventing pancreatic cancer" in claims 27 and 28 are merely suggestive of an intended use and are not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which are the polynucleotide or vector and pharmaceutically acceptable and carrier (see MPEP 2111.02).

GenBank Accession No. BQ71560 teaches a polynucleotide that encodes a polypeptide that has a sequence that is 100% identical to SEQ ID NO:2 of the instant application (see sequence search result #4, EST database, "20081001_131042_20081001_131042_us-10-529-592a-2.rst") and this polynucleotide was isolated from human salivary gland, epidermoid carcinoma. Given the polynucleotide BQ71560 encodes a polypeptide comprising an amino acid sequence having100% homology to SEQ ID NO:2 of the instant application, the polypeptide encoded would have biological activity equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2 as claimed.

GenBank Accession No. BQ71560 does not teach the polynucleotide harbored in a host cell or comprised in a vector, or producing the encoded polypeptide by culturing the host cell, expressing the polypeptide and collecting the polypeptide, or that the polynucleotide or vector are comprised in a composition with a pharmaceutically acceptable carrier.

Ausubel et al teach cloning and introducing genes into cells to analyze the genes' characteristics. Ausubel et al teach that researches are motivated to clone and express genes in cells in order to examine the gene's activity under different physiological conditions, examine gene expression, and to express the gene product for purification and biochemical characterization. Ausubel et al teach routine, conventionally used vectors for introducing a gene into isolated host cells for expression. Ausubel et al teach the DNA or vector are suspended in water or saline solution, which would be a pharmaceutically acceptable carrier (p. 9-2 through 9-14).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine a cDNA containing the polynucleotide of GenBank Accession No. BQ71560, with the methods of Ausubel et al to produce vectors for the expression of the polynucleotide because Ausubel et al teach that genes are conventionally expressed using a vector system in isolated host cells. One would have been motivated to make vectors comprising the polynucleotide of GenBank Accession No. BQ71560 in order to assay the functions of the polynucleotide in cells or to produce, isolate, and characterize the gene product. One of ordinary skill in the art would have a reasonable expectation of success making a vector comprising and

isolated host cell expressing the polynucleotide of GenBank Accession No. BQ71560, because methods of making vectors and isolated host cells expressing genes inserted into vectors are routine and conventional in the art.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine a cDNA or vector containing the polynucleotide of GenBank Accession No. BQ71560 with a pharmaceutically acceptable carrier such as water or saline because Ausubel teaches suspension of DNA in the carrier for transfection purposes. One would have been motivated to combine the GenBank Accession No. BQ71560 polynucleotide with water or saline in order to manipulate and store the polynucleotide for transfection studies and routine laboratory use. One of ordinary skill in the art would have a reasonable expectation of success combining the GenBank Accession No. BQ71560 polynucleotide with water or saline to make a composition because suspension and storage of DNA in these solutions is conventional practice.

14. **Conclusion:** No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642